

# Association Between ABO Blood Group System and COVID-19 Severity

## Case-Control Study From Libya

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### ABSTRACT

**Objectives:** A possible association between blood group systems (ABO and Rh) and coronavirus disease 2019 (COVID-19) severity has recently been investigated by various studies with conflicting results. However, due to variations in the prevalence of the ABO and Rh blood groups in different populations, their association with COVID-19 might be varied as well. Therefore, we conducted this study on Libyan participants to further investigate this association and make population-based data available to the worldwide scientific community.

**Methods:** In this case-control study, ABO and Rh blood groups in 419 confirmed COVID-19 cases in Zawia, Libya, and 271 healthy controls were compared using descriptive statistics and  $\chi^2$  tests.

**Results:** Blood group A was significantly more prevalent in patients with severe COVID-19 (64/125; 51.2%) than in patients with nonsevere COVID-19 (108/294, 36.7%) ( $P < .034$ ), whereas the O blood group prevalence was higher in nonsevere COVID-19 cases (131/294, 44.5%) compared with severe cases (43/125, 34.4%) ( $P < .001$ ).

**Conclusions:** The results showed a significant association between blood group A and the severity of COVID-19, whereas patients with blood group O showed a low risk of developing severe COVID-19 infection. No significant association was found between Rh and susceptibility/severity of the disease.

### INTRODUCTION

Since its outbreak, coronavirus disease 2019 (COVID-19) disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) continues to be a major public health threat. Globally, as of March 7, 2022, the disease has caused 440,807,756 confirmed cases, including 5,978,096 deaths.<sup>1</sup> In Libya, as of March 7, 2022, the cumulative cases reached 497,958 with 6,299 deaths according to the National Centre for Disease Control of Libya.<sup>2</sup>

### KEY POINTS

- There was a significant association between blood group A and COVID-19 severity.
- Patients with blood group O showed a low risk of developing severe COVID-19 infection.
- There was no significant association between Rh and COVID-19 severity.

### KEY WORDS

Blood groups; COVID-19; Rhesus antigen; Rh and disease severity; Libya

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Several studies have linked susceptibility to diseases with blood groups,<sup>3</sup> and a number of blood groups systems are recognized; however, ABO and Rh are the most widely used blood group systems in the world.<sup>4</sup> The association between ABO and Rh blood groups with various infectious diseases has been reported<sup>5</sup>; however, unlike the ABO blood group, Rh blood types are associated with fewer diseases.<sup>6</sup>

Recent studies from around the world have investigated the connections between ABO and Rh blood groups with SARS-CoV-2 infection. The understanding of blood group types and their relationship to COVID-19 severity might be useful in the disease management guidelines. However, as the relationship between the ABO and Rh systems may show variations between different populations,<sup>6</sup> their associations with COVID-19 might vary accordingly; therefore, we conducted this study to investigate this association further in Libyan participants with the primary goal of making population-based data available to outside researchers.

## MATERIALS AND METHODS

We retrospectively collected data from patients with confirmed COVID-19 who attended the main isolation center in the Zawia region of western Libya from December 1, 2020, to April 30, 2021. All retrieved data were from confirmed cases through real-time polymerase chain reaction (PCR). The real-time PCR analysis was performed in the COVID-19 laboratory in Zawia city. The rapid multiplexed real-time RT-PCR test, Xpert Xpress SARS-CoV-2/Flu/RSV, was used to simultaneously detect and differentiate between SARS-CoV-2, influenza A, influenza B, and respiratory syncytial virus (RSV) in the patients' nasopharyngeal swabs. The analysis runs on the Cepheid GeneXpert system according to the manufacturer instructions.

The ABO and Rh testing analysis was performed on the patients and the control group using a hemagglutination assay (Arena BioScien). Slide technique was used to detect the reaction of the antibodies, anti-A, anti-B, anti-AB, and anti-D antigens, for Rh testing indicating the presence or absence of the corresponding antigen in blood samples. The test was performed as per the manufacturer's instructions.

Data of patients without underlying comorbidities, such as diabetes, chronic lung disease, and cardiovascular diseases, and pregnant patients, were retrieved and included in the study to avoid the effect of these confounding variables on the analysis. The age of the participants ranged from 14 to 90 years. We were unable to verify some other risk factors such as obesity and smoking status due to lack of these data in patients' records.

We grouped the patients with COVID-19 in two groups according to the severity of their symptoms. The first group comprised patients with mild to moderate COVID-19 infection who tested positive by PCR and had a variety of signs and symptoms of COVID-19 but did not have dyspnea or abnormal chest X-ray, and their oxygen saturation (SpO<sub>2</sub>) was 94% or higher on room air. These patients, who were not hospitalized and advised to self-isolate at home, were followed up until recovery.

The second group comprised patients with severe and critical symptoms, who had a SpO<sub>2</sub> less than 94% on room air, had lung

infiltrates on chest X-ray or respiratory failure, and were admitted to the isolation center for intensive care and oxygen supplementation or mechanical ventilation. In addition, a control group was selected from healthy donors who attended the Zawia city blood bank from January 2021 to May 2021. The donors were selected independently regardless of their blood type status to minimize bias in selection. Eligible control individuals' selection criteria included people of similar ages and male-to-female ratio comparable to the patient group. The donors had no other history of respiratory infections such as tuberculosis and other infections and were negative for hepatitis B virus, hepatitis C virus, human immunodeficiency virus, and syphilis infections. In addition, donors with low weight or low blood pressure at the time of donation were excluded as per the Libyan blood banks' standard operating procedure. All patients and control group participants were unvaccinated against COVID-19 disease.

The Institutional Review Board of the Libyan Scientific Research Centre, Zawia, approved the study. The study was performed in accordance with the principles of the Declaration of Helsinki. The data of the patients were retrieved anonymously.

### Data Analysis

The distribution of the ABO blood group and Rh type among patients with COVID-19 and the control group was described using descriptive statistics, and a  $\chi^2$  test was used to highlight any statistically significant variables, where  $P < .05$  was considered statistically significant in all tests. Data analysis was undertaken using SPSS computer software for Windows (version 19; SPSS) and using the Microsoft Office Excel 2016 program.

## RESULTS

A total of 419 patients with COVID-19 and 271 control participants were included in this study. Most patients with COVID-19 had mild to moderate symptoms (70%) and were self-isolated at home. Only 29.8% of the study population developed severe symptoms and were admitted to the isolation center for intensive care and oxygen supplementation or mechanical ventilation.

The distribution of ABO blood groups among control individuals and patients with COVID-19 (severe and nonsevere) is outlined in **TABLE 1**. It was observed that most of the 125 severe cases were blood group A (51.2%) ( $P = .034$ ), followed by blood groups O (34.4%), B (10.4%), and AB (4.0%), respectively. In contrast, most of the 294 nonsevere cases were blood group O (44.5%) ( $P = .001$ ), followed by blood groups A (36.7%), B (12.5%), and AB (6.12%), respectively.

The percentage distribution of the ABO blood groups in the 271 control group participants (36.2%, 12.2%, 7.4%, and 44.3% for A, B, AB, and O, respectively) is comparable to that in nonsevere patients. Most of the patients with severe COVID-19 were male (64%) while the percentage of males in the nonsevere COVID-19 group was less (45.2%).

In this study, blood group B showed comparable percentages of 12.17%, 12.5%, and 10.4%, respectively, among control, severe, and nonsevere patient groups. In contrast, the AB blood group showed the lowest percentage among control, severe, and nonsevere patients groups: 7.4%, 6.1%, and 4.0%, respectively.

Most Libyan patients were Rh positive (87.8%), and only 12.2% were Rh negative. Both groups of patients had comparable percentages of Rh± blood type, with Rh+ accounting for most patients, and no significant association was found between Rh and susceptibility to the severity of disease **FIGURE 1**.

## DISCUSSION

Several studies from around the world have reported the possible association between the ABO blood group and the susceptibility to and severity of COVID-19 disease. However, some studies have shown conflicting findings.<sup>7</sup> Several medical conditions and risk factors have been identified and associated with the progression of COVID-19 into a severe and critical stage, including cardiovascular diseases, chronic lung diseases, diabetes, hypertension, tumors, liver and kidney diseases, immunodeficiency, and pregnancy, in addition to old age, male sex, obesity, and smoking.<sup>8</sup> However, to prevent the effect of the patients with associated medical conditions on the study analysis, we retrieved and

included data for patients with COVID-19 who had no associated medical conditions.

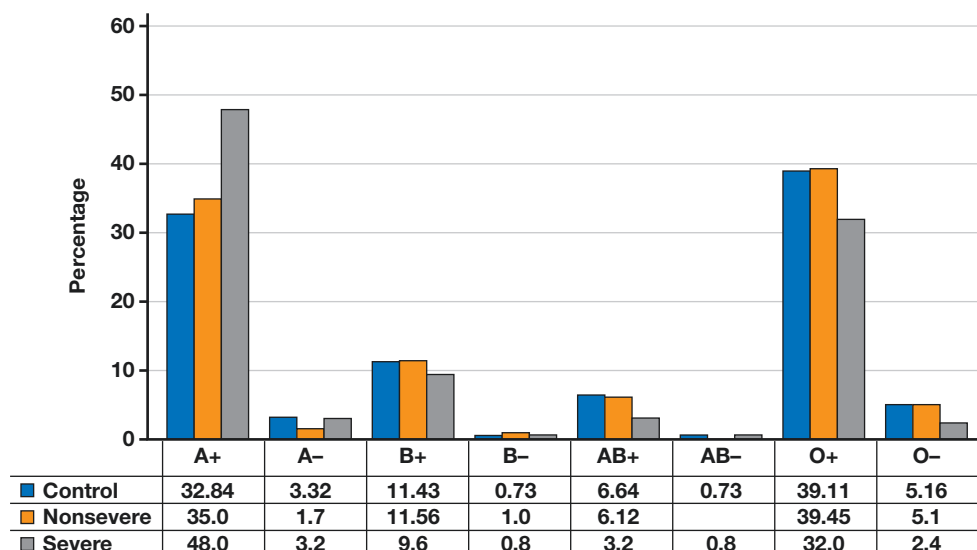
The prevalence of the ABO and Rh systems may differ among populations, and their linkage with the COVID-19 may differ too; therefore, in this study we examined the association of ABO blood groups and the severity of COVID-19 infection in participants from Libya.

In our study, patients with COVID-19 with blood group A were more likely to be admitted to the hospital with severe infection after contracting SARS-CoV-2, whereas patients with blood group type O had a decreased risk. Our findings were consistent with reports from previous studies on the topic from around the world.<sup>9-11</sup> Therefore, SARS-CoV-2 infection severity might be predicted according to the patients' blood group.

Unfortunately, due to lack of data, ABO distributions among those hospitalized with COVID-19 vs those hospitalized with non-COVID-19-associated conditions, or among infected survivors vs infected fatal cases, could not be investigated. As such, it cannot be extrapolated or discussed if a certain ABO group was associated with mortality and other non-COVID-19-associated conditions.<sup>12</sup>

**TABLE 1** Distribution of ABO Blood Groups Among Control Individuals and Patients With COVID-19

Characteristic	Control Group, No. (%)	Nonsevere Cases, No. (%)	Severe Cases, No. (%)	P Value
Total	271 (100)	294 (70.2)	125 (29.8)	
Male	144 (53.1)	133 (45.2)	80 (64.0)	
A blood group	98 (36.2)	108 (36.7)	64 (51.2)	.034
Male	50 (50.0)	50 (46.0)	41 (64.0)	
B blood group	33 (12.2)	37 (12.5)	13 (10.4)	.553
Male	19 (57.0)	15 (40.0)	10 (76.9)	
AB blood group	20 (7.4)	18 (6.1)	5 (4.0)	.396
Male	6 (30.0)	9 (50.0)	1 (20.0)	
O blood group	120 (44.3)	131 (44.5)	43 (34.4)	.001
Male	70 (58.3)	59 (45.0)	28 (65.0)	



**FIGURE 1** Percentage of ABO and Rh blood types among patients and control groups.

Studies have suggested several hypotheses for the underlying mechanisms of the association of the ABO blood groups and the susceptibility and severity of COVID-19.<sup>13</sup> A potential mechanism is the presence of receptors (induced by the ABO blood group system antigens) on host cells' surfaces, which could increase or decrease the ability of virus spikes to attach to the target host cells.<sup>14</sup>

Another possible mechanism is the existence of the natural anti-A and anti-B antibodies, which may reduce the severity and susceptibility of COVID-19 by either blocking the interaction between the viral spikes and the target cells' receptors and preventing the virus from attaching to host cells or eliminating the virus through opsonization. Therefore, people with blood group O may be less vulnerable to SARS-CoV-2.<sup>15-17</sup> Other studies proposed that the host transmembrane protease serine subtype 2 could play a significant role in modulating COVID-19 infection according to the ABO blood group system.<sup>18,19</sup>

## CONCLUSIONS

In conclusion, this study found a significant linkage between COVID-19 severity and distribution of the ABO blood groups. Patients with type A blood group are more likely to develop severe SARS-CoV-2 infection, whereas patients with type O blood group have a lower risk of developing severe SARS-CoV-2 infection. Further studies into the underlying molecular basis that makes people more or less susceptible to developing severe SARS-CoV-2 according to their ABO blood groups will help us understand and ascertain the correlation.

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